CBER Perspectives on Manufacturing Facility Design and Equipment for Processes Utilizing Mammalian Cell Culture

Williamsburg BioProcessing Foundation:
Facilities for Mammalian Cell Products
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Disclaimer:
Cell Derivation and Expression Construct

- **I will not focus on the characterization of constructs** or controls for laying down the master or working cell banks. FDA expectations are well described and specific concerns are better addressed during the pre-IND/IND phase.
  - *See "Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology (1985)"* http://www.fda.gov/cber/gdlns/ptcdna.htm
  - 1992 Supplement at http://www.fda.gov/cber/gdlns/ptcsupdna.pdf
  - 1996 FR Notice for ICH document describing analysis requirements for expression constructs in cells used for production of r-DNA derived protein products - available at http://www.fda.gov/cber/gdlns/ich_rdna.txt

Presentation Outline

- Emphasis on what CBER has found as being potential problem areas in bringing cell culture facilities on-line in the areas of:
  - Process design factors (*excluding cell construct issues*)
  - Equipment suitability assessment and validation
  - Lessons learned from inspectional findings
  - Avoiding problems down the road: Assessing risks during process development and design

Process Design – The Challenges

- Understanding the derivation history, stability of expression and productivity of the cells under the specified growth conditions – these should be thoroughly described.
- Understanding how cells respond to the microenvironments generated by the process equipment

Process Design – The Challenges

- The variety of manufacturing needs that cell culture operations address in getting diagnostic devices and therapeutics to clinicians for use
  - Various scales of rDNA proteins production
  - Cell culture to support viral propagation for virus based products
  - Patient individualized cell processing / cellular therapies

Growth Condition Effects

- During development phase, it is important to have a full understanding of cell behavior under varying growth conditions and to consider impacts as equipment systems are chosen…
- Possible concerns:
  - Cell responses to differing means of propagation (tank, perfusion, roller bottle, cell factories, etc.)
  - Potential impact of pressure changes on viability of attachment dependent cells
  - Microenvironment effects - localized differences in dissolved gases, nutrient availability, physicochemical measures (e.g., pH, osmolality, etc.)

Process Design

- Choice of growth conditions utilized combined with robustness of cell growth characteristics can greatly impact process output
- Choice of equipment supporting cell culture can impact on degree of control required
  - e.g., roller bottles require a number of aseptic manipulations that increase the possibility of contamination compared to tanks with steam-in-place addition/sampling ports

Process Design Factors - 1

- Examples:
  - Scale-up tank bioreactors -> changes in water column height; changes in pressure and potential impacts on cell attachment to carriers
  - New tank bioreactor -> changes in mixing dynamics, potential multiple toroid/toroid-like mixing patterns leading to poor nutrient or gas exchange uniformity
  - Changes in cell culture stress -> potential induction of endogenous retroviral particles

Process Design Factors - 2

- Examples (continued):
  - Adequate rate of perfusion for nutrients/gases and removal of wastes for hollow fiber systems?
  - Cell growth characteristics under perfusion conditions?
  - Variability of expression of recombinant protein constructs due to nutrient dynamics under perfusion versus tank growth conditions?

Equipment: Suitability Assessment and Validation - 1

- Capable of function under all intended physical conditions? (i.e., operating ranges for temperature, pressure, pH, etc)
- Capable of supplying the culture with needed nutrients, dO/dCO2 and environmental control?
- Capable of maintaining culture purity? (sterilizable input/sampling ports, sterile fluid addition capability, sanitary valves, etc)

Equipment: Suitability Assessment and Validation - 2

- Use of elastomeric contact materials
  - Glass transition temperature of the plastic and potential for brittleness with low temperature processing?
  - Tube welding process reproducible and robust?
  - Biocompatibility of elastomers, processing aids, lubricants, etc?
  - Adsorptive properties and impact on growth promoting characteristics of media (e.g., availability of cholesterol in serum free media)

Lessons Learned: Inspection (PAI) Findings

- The most common cell culture issues noted during PAIs are related to:
  - characterization of the cells and construct stability,
  - characterization of the product and any potential variability, and
  - maintaining purity of culture for cells or seeds.

Lessons Learned: Inspection findings

- The most common equipment issues noted during inspections (PAI and biennial) are related to:
  - equipment-related failures in processing,
  - failure to follow procedures (leading to process failure),
  - failures in quality unit responsibilities or functions, and
  - other pure GMP failures in manufacturing control

Lessons Learned: Inspection findings

- Many concerns not directly linked to manufacturing can be traced back to issues related to:
  - vague descriptions of procedures in documentation,
  - poor communications between various disciplines (e.g., process science, process engineering, facility engineering, quality operations, validation unit, etc.) while defining validation or fitness-for-use criteria, and/or
  - failure to take action when needed (sometimes due to unclear definition/understanding of responsibilities or authority to perform specific tasks)

How can we avoid some of these pitfalls?

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- Designing the process so that robust cell systems and production platforms can be supported
- Planning for the procedural controls that will be needed to implemented to maintain consistent process performance
- Identifying the weaknesses early in the design process so that mitigation can be built into the process

Assessing the Process: *"Risk Based Quality"*

- What does Quality mean?
  - "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." From the glossary of ICH Q6A
  - "Quality means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance." 21 CFR 820.3(s) *for medical devices*

Assessing the Process: "*Risk Based Quality*"

- Risk Management = dynamic and interactive use of Risk Assessment and Risk Mitigation
- Prospective *versus* Reactive Risk Assessment
  - Initial Process Mapping to outline initial validation plan and/or process control strategy
  - Problem identification process may be used by industry or regulators (e.g., deviation system or quality system inspections)
- *Relationship to Critical Process Parameters ?*

Relationship between validation and risk: What is Validation? - 1

- Validation is a requirement under cGMPs for finished pharmaceuticals, and considered requirements under Section 501(a)(2)(B) of FD&C for APIs (quote from Compliance Policy Guide 7132c.08)

Relationship between validation and risk: What is Validation? - 2

- "Process Validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications." Quote from 21 CFR 820.3(1) *for medical devices*
- Validation involves data collection

Relationship between validation and risk: What is Validation? - 3

- "Proof of validation is obtained through rational experimental design and evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase." (Compliance Policy Guide 7132c.08)
- How does one achieve "rational experimental design" ?
  - COMMUNICATION between organizational units and multi-disciplinary ANALYSIS of the specific operation

Is there really something new here?

- Yes and No
- ***Informal*** risk assessments have been performed for many years
- A more formalized risk assessment ***may*** assist in identifying possible hazards prior to initiation of developmental studies and/or validation/qualification studies AND provide a formal mechanism to encourage multi-disciplinary discussion and communication

Summary of Risk Assessment Approaches

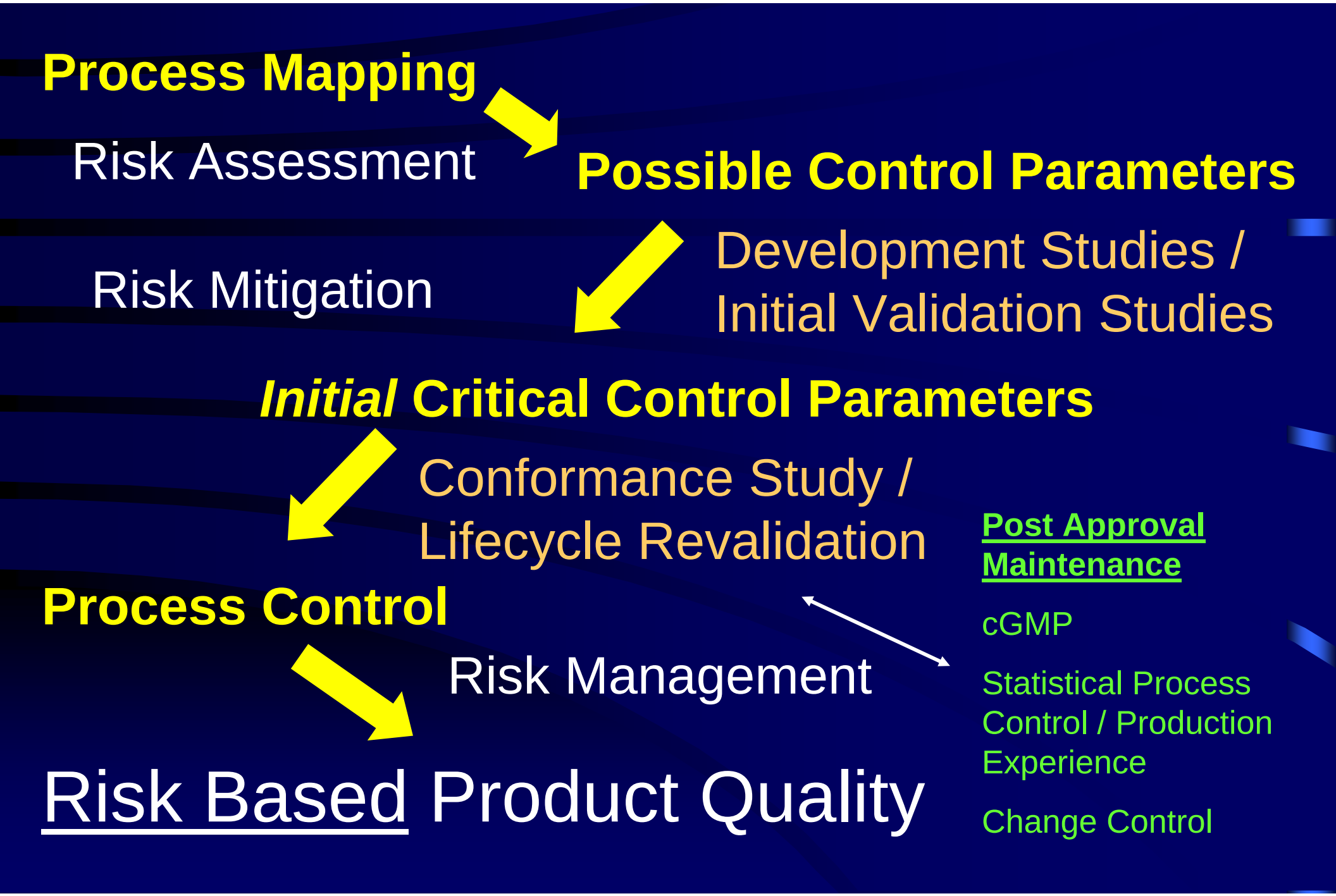
- Process Mapping is pre-requisite of risk assessment
- Various formalized approaches exist (e.g., PHA, HACCP, HAZOP, FTA, FMEA, FMECA, etc.) – Risk Management tools
- Risk Ranking and Filtering – compare and prioritize risks
- Supporting Statistical Tools (DOE, Process Capability Analysis, Control Charts, etc.)
- Informal Risk Management – *Why use more formalized approach?*

Some early priorities include:

- Prioritization of safety related qualification and validation activities
- Performing equipment capability assessments for each unit operation as processing parameters are defined
- Often new risk factors may be identified when equipment is undergoing initial usage, especially for emerging technologies where equipment performance and fitness-for-use criteria may not be well understood

Immediate Risk Related Concerns: Hazard Analysis and Evaluation

- Safety related issues:
  - Adventitious agents,
  - Maintaining sterility, culture purity, or bioburden control,
  - Immunogenicity concerns, etc.
- Process consistency:
  - Process alteration and optimization
  - Process scale up impacts
    - May be confounded by ongoing qualification and validation activities


Process Mapping
Risk Assessment
Possible Control Parameters
Risk Mitigation
Development Studies /
Initial Validation Studies
Initial Critical Control Parameters
Conformance Study /
Lifecycle Revalidation
Post Approval
Maintenance
Process Control
cGMP
Risk Management
Statistical Process
Control / Production
Experience
Change Control
Risk Based Product Quality

Risk Mitigation: Purpose of Testing

To verify that all processes and systems continue to function (as designed) on a routine basis …

AND

…that product meets quality expectations reflecting clinical experience.

Risk Mitigation: Testing Program

The process is dynamic and varies from product to product. For example:

- Suitability of raw materials
- Operating status of equipment/facility/personnel supporting a unit operation
- Suitability of material generated by a unit operation for continued production – you may want to include an approach including assessment of “end user requirements” in defining criteria for specific steps
- Suitability of final product for use


A QUALITY PRODUCT
QA/QC
Validation / Qualification
Routine Monitoring
Risk Assessment/Mitigation
Equipment
Environment
Process
Raw Materials
Components

Summary - 1

- Cell culture operations are complex and very dynamic, thus controlling the performance of the process requires understanding of the multiple variables and how they impact each other.
- Careful consideration during the process design stage can be very beneficial and contribute to successful implementation of a well-controlled and reliable production system.
- Variables impacted by multiple disciplines; therefore, multiple organizational units. Fostering open communication throughout process development will enhance ability to capture all critical aspects for validation and qualification activities earlier in the process (decrease needs for revalidation or managing non-conformance later in the process development cycle)

Summary - 2

- A structured risk management approach may assist in defining the important aspects to assess during early process development and subsequent validation activities
- Fitness-for-use criteria for equipment should be identified early in the process and based in early developmental studies to forego later complications
- FDA is open to discussions of specific aspects of process design throughout the product development cycle. Early communication with FDA is encouraged
- REMINDER: Once the process is designed and validated, robust quality unit required to oversee operations to ensure continued success. One of the major causes for compliance concerns after approval of a commercial process is shortcomings of a quality operations unit

Summary - 3

- In the future?
  - Q: What are the regulatory policy implications of improved testing methods?
  - Q: What are the regulatory policy implications of new cellular therapy source materials?
  - Q: What new challenges will emerging technologies bring to us all to deal with?

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